

# The Natural History of Surgically Treated Primary Adenocarcinoma of the Appendix

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## Objective

The aim of this investigation was to determine the prognostic variables and optimal surgical procedure for patients with adenocarcinoma of the appendix.

## Summary Background Data

Primary adenocarcinoma of the appendix is a rare malignancy that constitutes less than 0.5% of all gastrointestinal neoplasms. However, the prognostic factors and the preferred surgical procedure and outcome are poorly understood.

## Methods

The authors reviewed their institutional experience from 1976 to 1992 in treating 94 consecutive patients with primary adenocarcinoma of the appendix. Patients with carcinoid tumors or those in whom the diagnosis of primary cecal cancer could not be ruled out were excluded from the study.

## Results

Fifty-two (55%) patients had the mucinous variety, of which 22 had pseudomyxoma peritonei; the other 45% had the colonic and adenocarcinoid types of tumor. The most common presentation was that of acute appendicitis. Interestingly, in no patients was the correct diagnosis made before surgery, and it was entertained intraoperatively in only 30 patients (32%). The crude 5-year survival rate was 55%, but it varied with stage (A, 100%; B, 67%; C, 50%; and D, 6%;  $p < 0.01$ ) and with grade (I, 68%, and III, 7%;  $p < 0.01$ ). Patients with the mucinous type had a better prognosis than those with the colonic type ( $p < 0.01$ ). The survival rate was superior after right hemicolectomy *versus* appendectomy alone (68% vs. 20%,  $p < 0.001$ ). Right hemicolectomy performed as a secondary procedure resulted in the upstaging of 38% of the patients' tumors. A second primary malignancy occurred in 33 patients (35%), of which 17 were located in the gastrointestinal tract.

## Conclusions

Primary adenocarcinoma of the appendix should be treated by right hemicolectomy, even if it is a secondary procedure. Surveillance for synchronous or metachronous tumors, especially in the gastrointestinal tract, is warranted.

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Primary adenocarcinoma of the appendix is a rare neoplasm that constitutes less than 0.5% of all neoplasms of gastrointestinal origin.<sup>1</sup> Epithelial tumors of the appendix have been classified into four distinct types: carcinoids, mucinous adenocarcinoma (often called mucinous cystadenocarcinoma or malignant mucocoele), colonic-type adenocarcinoma, and adenocarcinoids with a dual cell origin. Carcinoid tumors account for 85% of the epithelial appendiceal tumors, followed in prevalence by mucinous adenocarcinoma, colonic-type adenocarcinoma, and the unusual adenocarcinoid type, which make up 8%, 4%, and 2%, respectively, of the cases.<sup>2-5</sup>

Because adenocarcinoma of the appendix (excluding the carcinoid tumors) is so rare, the clinical presentation and natural history are not well understood. To address this, we reviewed our experience in treating 94 consecutive patients with primary adenocarcinoma of the appendix encountered at our institution from 1976 through 1992. Patient characteristics, clinical presentation, methods of surgical therapy, prognostic factors, and survival will be discussed.

## METHODS

We reviewed the medical records of all patients with histologically proven neoplasms arising from the appendix between the years 1976 and 1992. Benign appendiceal mucocoeles, carcinoid tumors, and other nonepithelial tumors were carefully excluded according to previous criteria.<sup>6,7</sup> In brief, we looked for a continuity of the carcinoma with the appendiceal mucosa (to exclude cecal neoplasia) and for the presence of neoplastic acini containing mucin (thereby, excluding benign mucocoele). We excluded three patients in whom the diagnosis of cecal adenocarcinoma could not be excluded. The majority of patients ( $n = 56$ ) had their conditions diagnosed at our institutions; 38 were referred for further treatment after the diagnosis was made elsewhere. Multiple demographic, clinical, and laboratory parameters were collected with special emphasis on clinical presentation and diagnosis. Pathologic specimens were categorized into the type of neoplasm, grade, the Aster-Coller modification of the Dukes staging system, and the presence of appendiceal perforation and pseudomyxoma peritonei. The follow-up averaged 58 months (range, 1 to 194 months) and was 100% complete, either by our tumor registry or by direct patient contact. Survival plots were

constructed using a Kaplan-Meier analysis, and prognostic variables were determined using a Cox proportional-hazards regression analysis and a log-rank test.

## RESULTS

### Patient Population

During the 16 years from 1976 to 1992, we managed 94 patients with noncarcinoid adenocarcinoma of the appendix. Their mean age ( $\pm$  the standard error of the mean) was  $56.5 \pm 2$  years (range, 18 to 88 years); there were 52 men and 42 women. When grouped according to histologic type, 52 (55%) had a mucinous adenocarcinoma, 32 (34%) had the colonic type, and 10 (11%) had the adenocarcinoid type. There were no significant differences in age among the three groups. Although there was an overall male predominance, there tended to be more women in the adenocarcinoid group (eight women and two men).

### Clinical Presentation

The most common presentation was that of acute right lower quadrant pain, which was diagnosed as acute appendicitis in 47 patients (50%). Other presentations included a palpable mass in 13, ascites in 10, or nonspecific gastrointestinal or genitourinary complaints in 5. An additional 19 patients were being evaluated for an unrelated medical condition that required intra-abdominal surgery; at the time of surgery, the appendiceal neoplasm was found incidentally. A preoperative diagnosis of adenocarcinoma was not made in any patient, although it was one of the differential diagnoses in the ten patients with malignant ascites. Also, no patient had the preoperative diagnosis of a cecal neoplasm, which later proved to be an appendiceal tumor.

### Operative Procedure

The initial operative procedure included appendectomy alone in 59 patients—36 for presumed acute appendicitis, 19 as an unsuspecting incidental appendectomy during an unrelated intra-abdominal procedure, and 4 because of a palpable mass or presumed mucocoele in the appendix. By contrast, a right hemicolectomy was performed initially in 30 patients because of a presumed or pathologically confirmed appendiceal or other colonic neoplasm in 21 or because of presumed complicated appendicitis or cecal diverticulitis in 9. The remaining patients (all of whom had pseudomyxoma peritonei) underwent debulking of their tumors or a biopsy alone. Of the 59 patients initially undergoing appendectomy

Presented at the annual meeting of the American Society of Colon and Rectal Surgeons, Chicago, Illinois, on May 3, 1993.

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Accepted for publication April 28, 1993.

**Table 1. ADENOCARCINOMA OF THE APPENDIX: HISTOPATHOLOGIC STAGING**

Classification	All	Mucinous (52 patients)	Colonic- type (32 patients)	Adenocarcinoid (10 patients)
Staging*				
Dukes A	9 (10%)	4	4	1
Dukes B	37 (39%)	23	11	3
Dukes C	21 (22%)	10	8	3
Dukes D	27 (29%)	15	9	3
Grade†				
I	55 (59%)	36	13	6
II	22 (23%)	9	9	4
III	17 (18%)	7	10	0

None of the patients with mucinous adenocarcinoma had nodal, liver, or lung metastases. Staging represents the local wall invasion  $\pm$  adjacent organ involvement  $\pm$  peritoneal spread.

\* Aster-Coller modification.

† Broders grade.

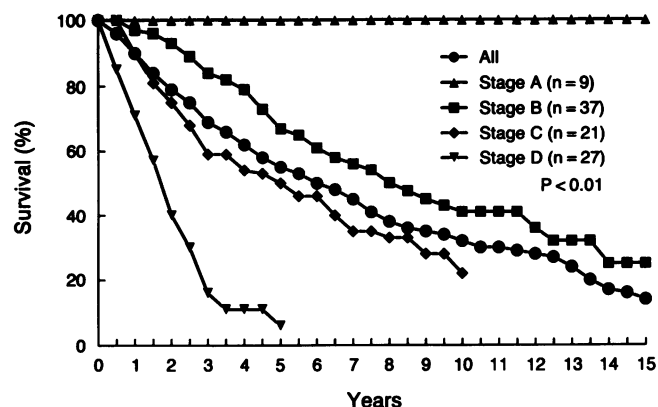
alone, 32 underwent subsequent reoperation and right hemicolectomy when the diagnosis became evident histopathologically. Overall, a perforated appendix was encountered in 43 patients (46%)—24 with mucinous adenocarcinoma, 18 with the colonic type, and 1 with the adenocarcinoid type. Pseudomyxoma peritonei was encountered in 22 patients (23%), all of whom, of course, had a mucinous adenocarcinoma. A synchronous second primary gastrointestinal malignancy (for which the operation was performed) was present in 11 patients (right colon, 7; sigmoid colon, 3; and pancreas, 1).

## Histopathologic Staging

About one half of the patients had disease localized to the bowel wall (Table 1) with 9 in a modified Dukes stage A (6 of whom had *in situ* disease), 37 in stage B, 21 in stage C, and 27 in stage D (distant metastases). The histologic variety did not affect the stage at presentation. By contrast, the histologic variety did affect the grade of differentiation. Most mucinous neoplasms were grade I (69%); the colonic type was equally distributed between grades I and III.

## Survival

With a mean follow-up of 56 months, the overall 5-year actuarial survival was about 55% (Fig. 1). Recurrent carcinoma developed in 40 patients after a mean of 23 months (range, 4 to 111 months). Currently, 41 patients



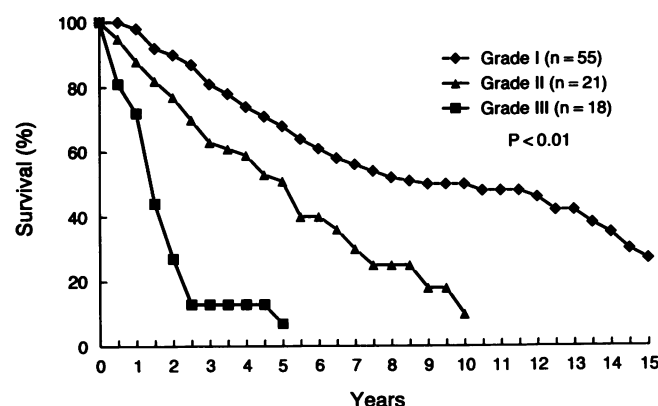
**Figure 1.** Actuarial survival of patients according to the Aster-Coller modification of Dukes staging for colonic cancer.

are still alive (mean follow-up, 87 months), of whom 27 have no evidence of disease.

The stage of the tumor significantly affected survival ( $p < 0.01$ ) with 5-year survival rates of 100%, 67%, 50%, and 6% for stages A, B, C, and D, respectively (Fig. 1). Similarly, the grade and histopathologic variety affected survival (Figs. 2 and 3). The 5-year survival rates were 68%, 51%, and 7% for grades I, II, and III, respectively ( $p < 0.01$ ). Patients with mucinous adenocarcinomas fared better than those with the colonic type with 5-year survival rates of 71% and 41%, respectively ( $p < 0.01$ ); those with adenocarcinoid tumors had intermediate rates (5-year survival rate, 55%).

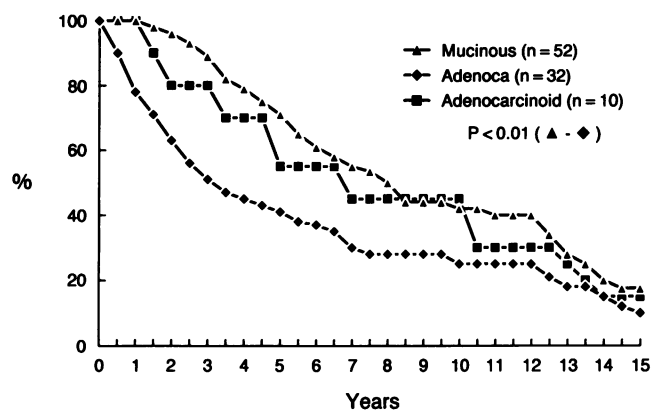
## Operative Management

We determined the survival rate according to the type of operative procedure. The 62 patients who underwent a right hemicolectomy, either as an initial or as a secondary procedure, did better than did the 27 patients who



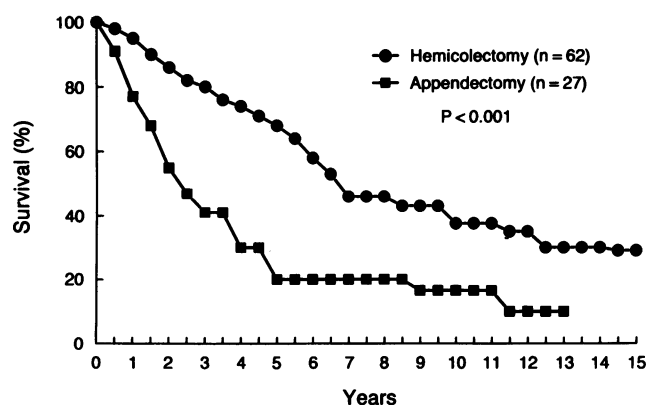
**Figure 2.** Actuarial survival of patients according to the histopathologic grade of the neoplasm.

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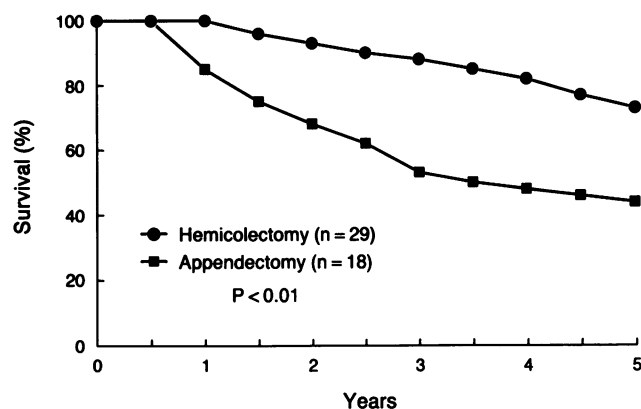


**Figure 3.** Actuarial survival of patients according to the histopathologic type of the appendiceal adenocarcinoma.

underwent appendectomy alone, with 5-year survival rates of 68% *versus* 20%, respectively ( $p < 0.001$ , Fig. 4). None of the patients who underwent appendectomy alone for either the colonic or adenocarcinoid type of tumor are alive currently. Also, in terms of tumor size, appendectomy alone as a treatment was not chosen on the basis of tumor progression because of the fact that 41% of the appendectomies were performed on potentially curable patients with stage A or B disease. Similar trends were found with the mucinous type; the data for the mucinous adenocarcinomas are shown in Figure 5 (only 7 of 18 patients who underwent appendectomy are still alive). When right hemicolectomy was performed as a secondary procedure (32 patients), the conditions of 12 patients (38%) were upstaged as a result of involvement of the lymph nodes in the mesentery. Simultaneous oophorectomy (for whatever reason) was carried out in 23 patients (12 with a mucinous type and 11 with a nonmucinous type), 13 of whom (57%) had ovarian metastases (7 with a mucinous type and 6 with a nonmucinous



**Figure 4.** Actuarial survival of patients according to the definitive operation performed.



**Figure 5.** Actuarial survival of patients with the mucinous type of appendiceal carcinoma according to the definitive operation.

type). The 5-year survival rate in patients with resected ovarian metastases was 31%.

## Second Malignancies

Second primary malignancies were encountered in 33 patients (35%, Table 2). Synchronous neoplasms occurred in 17 patients (18%), 11 of which were of gastrointestinal origin. Fourteen of these patients underwent abdominal operations, which actually led to the incidental diagnosis of the appendiceal neoplasm. Metachronous tumors developed in 16 patients (17%) after the diagnosis of the appendiceal neoplasm, of which 6 were of gastrointestinal origin.

**Table 2. SECOND PRIMARY MALIGNANCIES DEVELOPING IN PATIENTS WITH ADENOCARCINOMA OF THE APPENDIX**

Site	Synchronous	Metachronous	Total
Gastrointestinal	11	6	17
Colon	10	4	14
Rectum	—	2	2
Pancreas	1		1
Ovary	1		1
Uterus	1	1	2
Breast	1	3	4
Kidney	1		1
Prostate	1	1	2
Hematologic		2	2
Lung	1		1
Other*		3	3
Total	17	16	33

\* Thyroid, chondrosarcoma, melanoma.

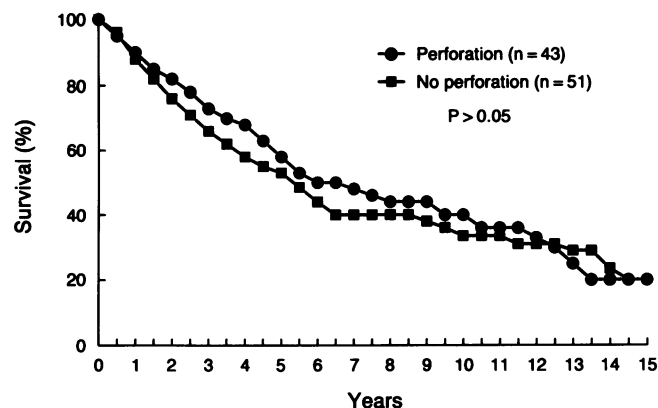
## DISCUSSION

Primary noncarcinoid adenocarcinoma of the appendix is a rare neoplasm with less than 300 cases reported worldwide.<sup>1,8,9</sup> Because a surgeon is unlikely to encounter more than a single case in his or her career, it is necessary to learn about the natural history of this unusual disease from the experience of referral centers. Our collected experience during the past 16 years with 94 patients has helped to delineate the range of the clinical presentation, pathologic stage, and prognosis. Moreover, this review offers several insights into the appropriate management of noncarcinoid appendiceal adenocarcinoma. Specifically, because the preoperative diagnosis is rarely evident, many patients will have the diagnosis made only several days after a simple appendectomy has been done by the review of the histopathologic specimen. Our study shows that these patients are best managed by reoperation and a formal right hemicolectomy because of the risk of overlooked nodal metastases (approximately 38%).

Comparisons of our collective experience with implications drawn from the literature show many similarities and a few differences that might be explained by other series with more anecdotal experience. Similar to colon cancer in general and primary adenocarcinoma of the appendix in particular as reported previously,<sup>1,10-12</sup> the mean overall age of our patients was 56 years with only 15% being younger than 40 years of age and only 1 patient being younger than 20 years of age. Unlike other smaller series, however, we found a slight male predominance but no clinically significant sex difference for any of the subtypes. These data agree with some previous reports<sup>9,11,12</sup> but contrast with the findings of other reports suggesting a 3:1 male predominance.<sup>1,13</sup>

The clinical presentation of the majority of our patients, and of those reported in the literature,<sup>1,8-18</sup> was that of acute appendicitis or an abdominal mass. Indeed, in none of our patients was an objective diagnosis of appendiceal neoplasm made before surgery, although it was entertained in the subgroup of ten patients identified with malignant ascites or presumed pseudomyxoma peritonei. Intraoperatively, the diagnosis was considered in only 30 patients (32%), again similar to the experience reported elsewhere. By contrast, the surgeon should maintain a high index of suspicion and, at least, entertain this diagnosis and/or urge an intraoperative frozen-section analysis in the patient who is older than 40 years of age when a mass in the wall of the appendix is appreciated.<sup>19</sup>

The anatomic peculiarities of the appendix lead to several interesting considerations in regard to appendiceal neoplasms. The narrow appendiceal diameter predis-



**Figure 6.** Actuarial survival of patients who had a perforated tumor vs. those without a perforation.

poses to occlusion of the lumen by the neoplasm early in its course.<sup>2,11</sup> With the mucinous adenocarcinoma variety, the lumen becomes distended with mucinous material and desquamated cells.<sup>10</sup> This situation leads to the potential for superimposed appendicitis and a marked tendency to rupture. Indeed, appendiceal adenocarcinoma represents the gastrointestinal neoplasm most commonly presenting with perforation.<sup>1,10,20</sup> In our series, appendiceal perforation was present in 46% of patients (56% with the colonic type). Another anatomic consideration is that the appendix often has deficiencies of both longitudinal and circular muscle fibers, which may not only predispose to perforation but also to apposition of the submucosa and the peritoneum, leading to the potential for early dissemination in seemingly non-advanced primary lesions.<sup>11,21,22</sup>

Whether perforation represents a poor prognostic factor, similar to the typical colonic carcinoma, remains controversial.<sup>17,21,23</sup> Perforation potentially leads to an earlier diagnosis and intervention<sup>1,2,15</sup> but may disseminate intraperitoneal tumor cells. We could demonstrate no statistical difference ( $p = 0.27$ ) when we compared the survival of the 43 patients who had perforated neoplasms with that of the other 51 patients who did not have perforations (Fig. 6). This may be related either to the less aggressive biologic behavior and better overall survival rate of the mucinous variety (even when associated with pseudomyxoma peritonei) or to a poorly understood biologic difference found in perforated appendiceal neoplasms, which may lead to a decreased tendency for peritoneal implantation. With the colonic type of appendiceal adenocarcinoma, it is probably the latter reason because perforated colonic neoplasms have a lower survival rate. At 5 years, the survival rate of our patients with the colonic type and perforation was 39% compared with 43% for those without perforation ( $p = 0.1$ ). The

mucinous type has a less aggressive behavior. Although there is a suggestion that patients with perforation fared better than those without perforation (74% *versus* 69% at 5 years and 48% *versus* 40% at 10 years), there was no statistical difference ( $p = 0.14$  and  $p = 0.08$ , respectively). Our findings suggest that perforation of an appendiceal adenocarcinoma does not necessarily alter the long-term prognosis.

Mucinous cystadenocarcinoma is usually a well-differentiated, slowly progressive neoplasm with pushing rather than infiltrating margins in which perforation will often result in pseudomyxoma peritonei, that is, peritoneal tumor implantation with free intraperitoneal mucous containing cellular elements.<sup>4,6,15,24</sup> Our series contained 52 patients with the mucinous type of appendiceal adenocarcinoma, 24 (46%) of whom had a perforated tumor at diagnosis and 20 (38%) of whom had intraperitoneal mucinous ascites when the diagnosis was made. However, only 14 patients (58% of those with perforation) had pseudomyxoma peritonei at diagnosis. Therefore, as also noted by others,<sup>10,13,20</sup> a perforated mucinous cystadenocarcinoma is not inevitably associated with the presence of pseudomyxoma peritonei, probably as a result of a localized sealing by the omentum or the inherent biologic characteristics of the neoplasm and its ability to implant on the peritoneum.<sup>6,13,25</sup> When we compared the actuarial 5-year survival rates, there was no statistical differences between those with and without pseudomyxoma (69% *vs.* 72%,  $p = 0.31$ ) or between those with both pseudomyxoma and perforation and those with pseudomyxoma but no frank perforation at diagnosis (71% *vs.* 67%,  $p = 0.22$ ). Therefore, the presence of pseudomyxoma alone or pseudomyxoma peritonei with perforation does not alter the prognosis.

Metastatic disease was encountered in 48 patients (51%, stages C and D). Some patients had metastases to more than one anatomic location or organ. The most common location was the peritoneal cavity, with either simple metastases or pseudomyxoma peritonei, followed by lymph nodes, liver, ovaries, abdominal wall, and lungs. No patient with mucinous adenocarcinoma of the appendix had lymph node, liver, or lung metastases. Although the colonic and adenocarcinoid types of tumor tend to spread lymphatically to ileocolic, infraduodenal, and para-aortic lymph nodes<sup>23</sup> and hematogenously to the liver or lungs, no lymphatic or blood-borne metastases were found in the mucinous type of primary appendiceal adenocarcinoma, even though major intraperitoneal disease may exist.<sup>6,8,13,14,24,25</sup>

Controversy exists concerning the preferred operation for primary noncarcinoid adenocarcinoma of the appendix. Although some of the older literature has claimed that appendectomy alone for grossly localized disease is

suitable treatment because the disease is basically a slow-growing, noninvasive process,<sup>10,26</sup> our findings and those of others<sup>18</sup> demonstrated that all of these appendiceal adenocarcinomas are invasive and that nodal metastases can be found in up to 45% of the colonic histologic types. In our experience, 17 of 42 patients with the colonic or adenocarcinoid variety had nodal metastases (40%). Thus, little debate should exist for patients with these subtypes in which the appropriate treatment involves a formal right hemicolectomy, even if it requires a reoperation in a patient who has undergone an appendectomy alone with disease ostensibly localized to the appendiceal wall (Dukes A and B lesions). The presence of nodal disease will identify those who may benefit from adjuvant chemotherapy with 5-fluorouracil and levamisole.<sup>27</sup>

By contrast, the indication for a formal right hemicolectomy in patients with the mucinous variety of appendiceal adenocarcinoma is more controversial. Theoretically, these neoplasms have no blood-borne or lymphatic tendency to metastasize, and simple appendectomy alone should be sufficient.<sup>8,10,26</sup> However, when we compared the 5-year actuarial survival rate of the 29 patients who had the mucinous variety and who underwent right hemicolectomy with that of the 18 managed by appendectomy alone, there was a survival advantage to colectomy (73% *vs.* 44%,  $p < 0.01$ , Fig. 5). This might be related to the presence of advanced pseudomyxoma peritonei in the latter group or to a more aggressive debulking in the former group. Moreover, several authors have noted some overlap in histologic findings between malignant mucocoele and the colonic type of appendiceal adenocarcinoma.<sup>1,10-12,15</sup> Therefore, unlike others,<sup>4,6,8,25,26,28</sup> we advocate an aggressive approach to the management of mucinous adenocarcinoma of the appendix with right hemicolectomy, debulking, and removal of all mucinous ascites in selected patients.<sup>11,15,20,29</sup> When near-total resection of all disease is possible in patients with pseudomyxoma peritonei, we continue to follow the approach of Sugarbaker et al.<sup>24</sup> and administer postoperative intraperitoneal chemotherapy, provided no gross or significant disease remains after resection and debulking.

In women, we also advocate routine oophorectomy (with all types of tumor), especially if they are postmenopausal. We found ovarian metastases in 13 of 23 patients subjected to oophorectomy. Although the prognosis is poor when ovarian metastases are present (mean survival, 30 months), oophorectomy is beneficial for staging, may prevent a potentially "privileged" site for symptomatic metastasis, and may prolong survival.<sup>4,5,16,30</sup> Indeed, the 5-year survival rate was 31% in this group of patients in whom metastatic ovarian disease was resected.

Finally, after a diagnosis of primary appendiceal adenocarcinoma has been made, a careful search for either a second synchronous neoplasm or a defined surveillance program for metachronous neoplasms during follow-up should be performed. As reported by others<sup>1,4,6,9,13,26,31</sup> and in our experience, there is a high incidence (35%) of second neoplasms, usually in the large intestine. This incidence of secondary neoplasms is much greater than that for colonic cancer in general.<sup>6</sup> Thus, in the patient undergoing re-exploration for right hemicolectomy after an initial appendectomy, a careful preoperative colonoscopy is warranted to detect the 12% prevalence of a synchronous colonic or rectal carcinoma. Likewise, a life-long program of subsequent postoperative colonic surveillance also should be instituted. For other noncolonic, second primary malignancies associated with adenocarcinoma of the appendix (Table 2), we recommend performing computed tomography to search for these before surgery (synchronous tumors) or during follow-up (metachronous tumors).

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